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Factors associated with HIV Disease Progression in Discordant Couples, Rwanda 2002-2012

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Rollins School of Public Health

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Abstract

Factors associated with HIV Disease Progression in Discordant Couples, Rwanda 2002-2012

By Ayano Annis

Background: It is unknown why disease progression happens slower or faster than other people. There are studies that suggest different exposures, such as co-infections, women's hormonal injectable contraception use, increased age could change HIV disease progression speed.

Methods: From 1994 to 2012, HIV discordant couples were recruited from Kigali, Rwanda to receive couples' HIV counseling and testing services and were followed up every 3 months. Multivariable analysis were used to determine associations between different exposures and three HIV disease progression outcomes: (1) time to all-cause death among HIV positive partners, (2) time to ART initiation among HIV positive partners, and (3) a composite of the prior two outcomes.

Results: When comparing HIV+ males and HIV+ females of couples, we found that the outcome of death had similar rates, but HIV+ females had higher rates of initiating ART therapy than HIV+ males. This led to the combined outcome of disease progression to be higher in HIV+ females than HIV+ males.

For HIV+ males, age, was found to be associated with HIV progression in the multivariate analysis. HIV stage and genital inflammation was found to be associated with disease progression in the univariate analysis. We did find additional associations of extrapulmonary TB and ESR with disease progression in the multivariate analysis including missingness variables, but it is unknown if these associations truly exist.

In the HIV+ females, there was an association between date of enrollment, age, HIV stage, pregnancy status, and genital inflammation. In the univariate analysis, the previous stated exposures, method of contraception and genital ulceration were also found to be associated with disease progression. There were small samples sizes for those who progressed and had high log viral load or had TB, but multivariate associations were found when including missingness variables. These associations may be questionable.

Conclusions: We need further studies to understand why males are not initiating ART as much as females are. Implant, injectables, and OCPs are safe for HIV-infected women to use to prevent pregnancy. Higher ART for pregnant women prevents mother to child transmission.

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Chapter 1

Literature Review

HIV/AIDS History and Disease

HIV/AIDS first appeared in the United States in the early 1980s, appearing as pneumonia ((CDC), 2017). Initial reports led to stigma towards certain populations as more research was done on this disease. HIV/AIDS is now known as a sexually transmitted disease, which can spread through other bodily fluid, such as blood. Although much is known about how HIV/AIDS is transmitted and there are treatment options, it is still a public health issue. As of 2018, there are approximately 37.9 million people living with HIV worldwide (WHO, 2019). In much of the world, HIV is now a chronic disease instead of a death sentence since antiretroviral therapy (ART) has become more readily available. ART was introduced in high-income countries in 1998 and to lower-income countries in 2002 (Richardson, Grant, & Zolopa, 2014). Many studies have shown that HIV progression is different from person to person (Al-Jabri, 2007; Tough & McLaren, 2018). HIV infection works in different phases. At the start of HIV infection, CD4+ counts decrease and HIV viral load increases, which is known as the acute phase. During the latent phase, for a brief period, an infected individual's CD4+ counts increase before decreasing further, while viral load also decreases. The progression into AIDS shows a low CD4+ count and high viral load (Tough & McLaren, 2018). There are several factors which have been predicted to be associated with HIV disease progression.

Pregnancy

One factor which does not have scientific agreement if is associated with HIV disease progression is pregnancy. One study measured disease progression is CD4+ counts, as a lower CD4+ count is indicative of disease progression (Wall, Rida, et al., 2017). It found that CD4+ decreases slightly during pregnancy, but tends to rebound to pre-pregnancy levels after (Wall, Rida, et al., 2017). They also found in a previous study that pregnancy was not related to death in HIV+ women (Wall et al., 2016).A systematic review overall found that pregnancy was not associated with disease progression, but there were three studies that did find associations with pregnancy and disease progression (Calvert & Ronsmans, 2015). The definition of disease progression for HIV with the studies found in the systematic review were progression to HIV-related illness, progression to AIDS-defining illness, HIV-related death, any death, and drop in CD4+ cell count. The different disease progression outcomes may change whether pregnancy is associated that disease progression outcome.

Contraception

Another factor which also does not have scientific agreement is the association between different contraception techniques and disease progression. One study found that implant contraception and injectables were protective of disease progression, while oral contraception was not (Wall et al., 2016). A systematic review agrees with the previous study that injectables were associated with protection of disease progression and oral contraception was not associated (Phillips, Polis,

& Curtis, 2016). This is contrary to another study which did not find an association between hormonal contraceptives (oral, IUDs, and DMPA) and disease progression among women who were not currently on ART (Whiteman et al., 2016).

Other

There are several other factors found in other studies that are related to disease progression. One study on a cohort of drug users found that age and marital status was associated with disease progression, while HAART (high action antiretroviral therapy) and condoms were associated with decreased risk of disease progression (Luo, Sun, & Du, 2019). Age was likely related because the longer an individual lives with HIV without treatment, the more likely they are to progress with AIDS (Luo et al., 2019). For marital status, they found that single people were less likely to progress to AIDS, while married people were more likely and it was not entirely known why except for behavioral reasons (Luo et al., 2019). One systematic review looked at molecular differences between HIV infected individuals and one that was found to increase time to progress to AIDS or stop the progression entirely is CCR5Δ32 (Tough & McLaren, 2018). Another study says the CCR-5 receptor is how HIV enters into the cell, so the deletion of this receptor will not allow HIV to infect a cell and begin infection (Al-Jabri, 2007). There may also be different immune responses, such as CD8+ responses, that may be associated with longer disease progression (Al-Jabri, 2007).

Chapter 2

Introduction

As of 2018, 37.9 million people were living with human immunodeficiency virus (HIV) (WHO, 2019). Living with HIV was initially a death sentence, as the disease would further progress into acquired immunodeficiency syndrome (AIDS). With the introduction of antiretroviral therapy (ART) in 1998 for high-income countries and 2002 for lower-income countries, HIV has started becoming to be a chronic disease (Richardson et al., 2014).

Some people progress from HIV to AIDS at a slower time than others. Disease progression from HIV to AIDS is tracked by CD4+ counts and other co-infections, such as tuberculosis. At the start of HIV infection, CD4+ counts decrease and HIV viral load increases, which is known as the acute phase. During the latent phase, for a brief period, an infected individuals CD4+ count increases before decreasing, while viral load also decreases. The progression into AIDS is characterized by a low CD4+ count and high viral load (Tough & McLaren, 2018).

It is not entirely known why some individuals progress faster than others, but there may be biological or environmental factors. One biological example is the deletion of the gene CCR-5, which has been found to be associated with slow or no disease progression. This mutation is found within 1% of the Caucasian population, but has not been found in African populations (Al-Jabri, 2007). Several studies and meta-analysis/systematic reviews have shown women’s hormonal and injectable contraception use, increased age, and co-infections (hepatitis C and STDs) being associated with disease progression (Al-Jabri, 2007; Calvert & Ronsmans, 2015;

Luo et al., 2019; Polo et al., 2019; Wall et al., 2016). Understanding the factors associated with disease progression may help determine behavioral changes those with HIV can undertake or clinical factors that providers can intervene on to slow disease progression. In this study evaluate factors associated with HIV disease progression, defined as death or introduction to ART therapy in a longitudinal cohort of heterosexual serodiscordant couples in Rwanda.

Methods

Ethics

Approvals were given by the Office for Human Research Protections registered in the Institutional Review Boards at Emory University and in Zambia. All couples who participated were provided written consent.

Participants

The methods used by the Rwanda Zambia HIV Research Group (RZHRG) for study recruitment, eligibility, follow-up, and data collection have been previous published (Wall et al., 2016). Briefly, participant couples were recruited from Kigali, Rwanda to receive couples' voluntary HIV counseling and testing services. Only heterosexual HIV-1 discordant couple pairs were included in this study. The couples were followed up every 3 months between 1994 and 2012 and were censored if they were lost to follow-up, the negative partner seroconverted, or they had separated. A rapid serologic HIV test was conducted at baseline and every 3 months for negative partners to determine if that partner had seroconverted. The primary objective of this analysis was to determine if there was an association between different exposures and disease progression of HIV for the partner positive for HIV.

Baseline Exposures

Baseline exposures were measured at the couple's first visit. Age, monthly family income, number of living children, and viral load were assessed as continuous measures. The WHO guidance for ART initiation has changed throughout the 2000s, which is why date of enrollment was looked at as a possible factor for disease progression. This variable was categorized into four groups (2002-2004, 2004-2006, 2006-2008, 2008-2011). Dichotomous variables included HIV-1 positive partner having drunk alcohol in the last year, desiring more children, having a sexually transmitted infection (STI) in the past year, and Kinyrwanda literacy. For men who were HIV positive, self-reported circumcision status was also measured. HIV stage was limited to only 1, 2, and 3 as there were no Stage 4 participants. HSV-2 status was categorized as positive, negative, and inconclusive.

Time-varying Exposures

Time-varying exposures could change as participants were followed-up. Erythrocyte sedimentation rate (ESR), a non-specific measure of systemic inflammation, per unit increase was a continuous variable in the data analysis. TB was treated as its own variable as well as categorized into extrapulmonary and pulmonary TB. Genital inflammation was categorized into

STI-associated inflammation, non-STI inflammation, and no genital inflammation. STI-inflammation was defined as clinical/laboratory diagnosis or treatment of gonorrhea, chlamydia or trichomonas (Wall, Kilembe, et al., 2017). Non-STI inflammation was any observed/reported discharge, dysuria, dyspareunia, and/or laboratory diagnosis of candida or BV (Wall, Kilembe, et al., 2017). Inflammation was measured by self-report (genital ulcer, urethral or vaginal discharge, dysuria or dyspareunia), internal and external genital examination (redness, swelling, exudate, discharge, irritation or tenderness), and laboratory tests (RPR; BD Macro-Vue, Becton-Dickinson Europe, with Treponema pallidum hemagglutination assays (TPHAs)) (Wall, Kilembe, et al., 2017). Genital ulceration and bilateral inguinal adenopathy were treated as yes/no responses. For HIV positive women, the method of contraception (non-hormonal, implant, injectables, oral contraceptive pills [OCPs]), pregnancy, and breastfeeding were used as exposures.

Outcomes

There were three different disease progression outcomes: (1) time to all-cause death among HIV positive partners, (2) time to ART initiation among HIV positive partners, and (3) a composite of the prior two outcomes. In Rwanda, ART was not readily available before 2003, so those who enrolled beforehand could not have ART initiation until 2003. Therefore, analyses of ART initiation is restricted to November 2003 to 2012. If ART initiation came before death, time to outcome is censored at ART initiation.

Data Analyses

Data analysis was conducted with SAS v9.4 (Cary, NC). Outcome rates were measures per 100 person years with corresponding 95% confidence intervals. Crude hazard ratios (HR) were estimated using bivariate Cox models for each exposure and 95% confidence intervals (CIs) and two-sided P values are shown (Table 2a, b). Exposures which were found to be significant in bivariate analyses were then used in multivariable Cox models. The model was assessed for multi-collinearity issues. All analyses are stratified by the gender of the HIV-positive partner.

Results

HIV Disease Progression Rates (Table 1)

Overall, 884 discordant couples in which the man was the HIV+ partner (M+F-) were followed for 1707.9 person years and 973 discordant couples in which the woman was the HIV+ partner (M-F+) were followed for 1851.6 person years. HIV+ men died at a rate of 2.05/100PY (95%CI 1.57, 2.53), which was higher than the mortality rate of HIV+ women (1.67/100PY, 95%CI 1.26, 2.09). The rate of ART initiation among HIV+ men was 0.70/100PY (95%CI 0.42, 0.98). The rate of ART initiation among HIV+ women was 16.36/100PY (95%CI 15.18, 17.55). HIV+ men had a combined outcome rate of death and ART initiation of 2.75/100PY (95%CI 2.20, 3.30). For HIV+ women, this rate was 17.82/100 PY (16.60, 19.05).

Bivariate analyses: Factors Associated with HIV Disease Progression (Table 2a, b)

In bivariate analyses among HIV+ men, older age (HR = 1.04 95%CI 1.00, 1.07) and extrapulmonary TB (HR = 12.14 95%CI 1.54, 95.78) were statistically significant factors associated with disease progression. Additionally, STI-related inflammation increased rates of HIV disease progression (HR = 3.89 95%CI 1.17, 12.96) as did men with HIV stage 3 vs stage 1 (HR 2.06 95%CI 1.03, 4.14).

In bivariate analyses among HIV+ women, older age (HR = 1.03 95%CI 1.01, 1.04), higher log viral load (HR = 1.71 95%CI 1.34, 2.18), being pregnant (HR = 3.34 95%CI 2.54, 4.40), higher ESR (HR = 1.01 95%CI 1.01, 1.02), pulmonary TB (HR = 4.48 95%CI 1.65, 12.17), extrapulmonary and pulmonary TB (HR = 3.24 95%CI 1.19, 8.81), genital ulceration (HR = 1.53 95%CI 1.08, 2.17), current breastfeeding (HR = 0.57 95%CI 0.38, 0.86), later date of enrollment after 2008 vs earlier enrollment before 2004 (HR = 2.07, 95%CI 1.21, 3.55) were found to be significant exposures. Additionally, compared to HIV+ women who were HIV stage 1, those in stage 2 (HR = 1.62 95%CI 1.26, 2.10) and stage 3 (HR = 2.43 95%CI 1.84, 3.22) were more likely to progress. Compared with women using non-hormonal contraception, women who were using injectables were less likely to progress (HR = 0.64 95%CI 0.43, 0.95). Those with STI inflammation (HR = 1.62 95%CI 1.08, 2.43) and non-STI inflammation (HR = 2.90 95%CI 1.81, 4.65) were more likely to progress compared with those with no inflammation.

Multivariate Analyses: Factors Associated with HIV Disease Progression (Table 3a, 3b, 4a, 4b)

For the model of HIV disease progression in HIV+ men and HIV+ women, no collinearity issues were found. For the HIV+ men model, the inflammation variable was changed to only include STI inflammation because there was nobody who progressed who had non-STI inflammation. For HIV+ women model, the pulmonary TB variable was dropped while TB was kept.

In the multivariable analysis of HIV+ men and disease progression, we found the aHR associated with men's age was 1.03 (95%CI 1.00, 1.07). Compared with HIV+ men who were HIV stage 1, those in stage 2 had an aHR of 0.81 (95%CI 0.37, 1.80) and those in stage 3 had an aHR of 1.72 (95%CI 0.84, 3.53). Additionally, compared to those with no inflammation those with STI-related inflammation had an aHR of 3.30 (95%CI 0.97, 11.21). Running a model including variables with more than 20% missingness shows extrapulmonary TB was associated with disease progression with an aHR of 0.08 (95%CI 0.01, 0.65). ESR was also found to be associated with disease progression with an aHR of 1.03 (95%CI 1.02, 1.04).

In the multivariable analysis for HIV+ women, being older (aHR 1.02 95%CI 1.00, 1.04), being pregnant (aHR 3.12 95%CI 2.33, 4.17) and having STI-related inflammation (aHR 2.22 95%CI 1.30, 3.79) was related to disease progression. Additionally, a woman in stage 3 HIV was more likely to progress than a woman in stage 1 (aHR 2.40 95%CI 1.77, 3.26) and those in stage 2 HIV are also more likely to progress than a woman in stage 1 (aHR 1.65 95%CI 1.26, 2.18). Including variables with 20% missingness, higher log viral load (aHR 1.67 95%CI 1.25, 2.24)

and having TB (aHR 24.31 95%CI 2.35, 252.03). The aHR of disease progression and breastfeeding was 0.27 (95%CI 0.04, 1.96).

Table 1. Disease progression outcome rates

	M+ (N = 884)				
	N Outcomes	PY at risk	Outcome / 100 PY	95%CI	
Deaths	**35**	**1707.9**	**2.05**	1.57	2.53
ART initiations	**12**	**1707.9**	**0.70**	0.42	0.98
Deaths + ART initiations	**47**	**1707.9**	**2.75**	2.20	3.30
	F+ (N = 973)				
	N Outcomes	PY at risk	Outcome / 100 PY	95%CI	
Deaths	**31**	**1851.6**	**1.67**	1.26	2.09
ART initiations	**303**	**1851.6**	**16.36**	15.18	17.55
Deaths + ART initiations	**330**	**1851.6**	**17.82**	16.60	19.05

CI: confidence interval
ART: antiretroviral treatment
PY: person-year
Deaths: $p = 0.415$
ART initiations: $p < 0.0001$
Deaths + ART initiations: $p < 0.0001$
p values are 2 tailed Mid-P exact

Table 2a. Univariate associations between covariates and disease progression for men

	M+							
	Progressed		Did not progress		HR	95% CI		p-value
	N intervals	%	N intervals	%				
Baseline measures								
Date of enrollment								
2002-2004	15	0.3	1402	0.17	ref			
2004-2006	19	0.4	3263	0.39	1.00	0.43	2.09	0.997
2006-2008	9	0.2	1609	0.19	1.30	0.42	4.02	0.648
2008-2011	4	0.1	2124	0.25	1.13	0.27	4.77	0.870
Age (per year increase) [mean(stdev)]	39	8.4	36.2	7.60	1.04	1.00	1.07	0.050
Monthly family income (per USD increase) [med(intquart)]	38	42.5	50	56	1.00	1.00	1.00	0.587
Reads Kinyrwanda								
Yes	35	0.8	7418	0.86	0.65	0.31	1.36	0.253
No	9	0.2	1209	0.14	ref			
Drunk in the last year								
Yes	16	0.4	3045	0.35	0.90	0.49	1.66	0.735
No	28	0.6	5582	0.65	ref			
Number of living children [mean(stdev)]	1.7	1.0	2.16	1.79	0.82	0.56	1.20	0.302
Desire for more children^								
Yes/Don't know	3	0.1	508	0.09	1.06	0.32	3.48	0.921
No	33	0.9	5221	0.91	ref			
HIV stage*								
Stage I	14	0.3	3140	0.36	ref			
Stage II	14	0.3	3750	0.43	0.97	0.46	2.04	0.935
Stage III	19	0.4	1741	0.20	2.06	1.03	4.14	0.043
Log viral load (per log10 copies/ml increase) [mean(stdev)]^	4.6	1.1	4.05	1	2.50	0.93	6.74	0.069
STI in the past year								
Yes	19	0.5	3151	0.38	1.10	0.59	2.03	0.766
No	23	0.5	5157	0.62	ref			
HSV-2 status^								
Positive	18	0.6	5062	0.60	0.97	0.39	2.45	0.951
Inconclusive	4	0.1	1831	0.22	0.52	0.15	1.83	0.307
Negative	6	0.2	1602	0.19	ref			
Men's circumcision status								
Circumcised	13	0.3	1397	0.20	1.86	0.98	3.53	0.058
Not circumcised	34	0.7	7233	0.84	ref			
Time-varying measures								
ESR (per unit increase) [med(intquart)]^			40	31.53	1.03	1.02	1.04	<.0001
Extrapulmonary TB^								
Yes	1	0.029	10	0.00	12.14	1.54	95.78	0.018
No	33	0.971	4666	1.00	ref			
Pulmonary TB^								
Yes	1	0.029	43	0.01	1.76	0.24	13.11	0.580
No	33	0.971	4633	0.99	ref			
TB^								
Yes	2	0.059	52	0.01	3.17	0.75	13.44	0.119
No	32	0.941	4624	0.99	ref			
Genital Inflammation								
Yes (STI) 2	3	0.07	106	0.01	3.89	1.17	12.96	0.027
Yes (non-STI) 1	0	0	4	0.00	0.00	0.00	.	0.988
No	40	0.93	7218	0.98	ref			
Genital ulceration^								
Yes	2	0.057	486	0.10	0.51	0.12	2.15	0.357
No	33	0.943	4479	0.90	ref			
Bilateral inguinal adenopathy^								
Yes	3	0.25	511	0.37	0.65	0.16	2.56	0.536
No	9	0.75	874	0.63	ref			

HR: hazard ratios from univariate Cox models
CI: confidence interval
ART: antiretroviral treatment
p-values are 2-tailed from univariate Cox models
Skew cutoff of 1
*No members had Stage IV HIV
^Contains more than 20% missing

Table 2b. Univariate associations between covariates and disease progression for women

	F+							
	Progressed		Did not progress		HR	95% CI		p-value
	N intervals	%	N intervals	%				
Baseline measures								
Date of enrollment								
2002-2004	51	0.16	1417	0.19	ref			
2004-2006	106	0.33	3662	0.48	0.79	0.54	1.14	0.206
2006-2008	86	0.27	1477	0.20	1.45	0.95	2.22	0.861
2008-2011	78	0.24	1007	0.13	2.07	1.21	3.55	0.008
Age (per year increase) [mean(stdev)]	30	5.97	29.2	6.06	1.03	1.01	1.04	0.006
Monthly family income (per USD increase) [med(intquart)]	50	54.2	43.2	46.5	1.0	1.0	1.0	0.471
Reads Kinyrwanda [contains 3 groups?]								
Yes	255	0.77	5653	0.74	1.17	0.91	1.52	0.224
No	75	0.23	1963	0.26	ref			
Drunk in the last year								
Yes	21	0.06	492	0.06	1.01	0.65	1.58	0.952
No	309	0.94	7124	0.94	ref			
Number of living children [mean(stdev)]	1.3	1.46	1.5	1.40	0.89	0.77	1.03	0.109
Desire for more children^								
Yes/Don't know	16	0.08	455	0.07	0.92	0.54	1.55	0.742
No	195	0.94	5865	0.93	ref			
HIV stage*								
Stage I	107	0.32	3603	0.47	ref			
Stage II	129	0.39	2630	0.35	1.62	1.26	2.10	0.0002
Stage III	94	0.28	1385	0.18	2.43	1.84	3.22	<.0001
Log viral load (per log10 copies/ml increase) [mean(stdev)]^	4	1.03	3.6	1	1.71	1.34	2.18	<.0001
STI in the past year								
Yes	189	0.58	4069	0.56	1.16	0.93	1.45	0.192
No	136	0.42	3218	0.44	ref			
HSV-2 status								
Positive	242	0.79	5376	0.72	1.03	0.74	1.44	0.843
Inconclusive	22	0.07	1150	0.15	0.52	0.31	0.09	0.013
Negative	42	0.14	941	0.13	ref			
Time-varying measures								
Pregnancy status								
Pregnant	67	0.22	543	0.076	3.34	2.54	4.40	<.0001
Not pregnant	242	0.78	6596	0.924	ref			
Method of contraception								
Non-hormonal**	283	0.86	6124	0.822	ref			
Implant	17	0.05	332	0.045	0.68	0.40	1.17	0.162
Injectables	27	0.08	858	0.115	0.64	0.43	0.95	0.028
OCPs	3	0.01	133	0.018	0.40	0.13	1.26	0.119
ESR (per unit increase) [med(intquart)]^	58.9	32.66	52.14	28.87	1.01	1.01	1.02	<.0001
Extrapulmonary TB^								
Yes	0	0.0	12	0.0	0	0	.	0.978
No	214	1.0	4990	1.0	ref			
Pulmonary TB^								
Yes	4	0.02	24	0.0	4.48	1.65	12.17	0.003
No	210	0.98	4978	1.0	ref			
TB^								
Yes	4	0.02	32	0.007	3.24	1.19	8.81	0.021
No	198	0.98	4334	0.993	ref			
Genital Inflammation								
Yes (STI) 2	26	0.08	6943	0.926	1.62	1.08	2.43	0.019
Yes (non-STI) 1	19	0.06	164	0.022	2.90	1.81	4.65	<.0001
No	285	0.86	390	0.052	ref			
Genital ulceration								
Yes	39	0.12	718	0.097	1.53	1.08	2.17	0.017
No	284	0.88	6697	0.903	ref			
Bilateral inguinal adenopathy^								
Yes	26	0.18	303	0.178	1.17	0.75	1.82	0.498
No	117	0.82	1398	0.822	ref			
Breastfeeding^								
Yes	25	0.09	780	0.146	0.57	0.38	0.86	0.008
No	267	0.91	4552	0.854	ref			

HR: hazard ratios from univariate Cox models
CI: confidence interval
ART: antiretroviral treatment
p-values are 2-tailed from univariate Cox models
Skew cutoff of 1
*No members had Stage IV HIV
^Contains more than 20% missing

Table 3a. Multivariate associations between covariates and disease progression for men

	M+			
	aHR	**95% CI**		**p-value**
Age (per year increase)	1.03	1.00	1.07	0.081
HIV stage*				
Stage I	ref			
Stage II	0.81	0.37	1.80	0.606
Stage III	1.72	0.84	3.53	0.137
Genital Inflammation				
Yes (STI)	3.30	0.97	11.21	0.056
No	ref			

aHR: hazard ratios from univariate Cox models
CI: confidence interval
p-values are 2-tailed from univariate Cox models
*No members had Stage IV HIV
47 outcomes modeled

Table 3b. Multivariate associations between covariates and disease progression for women

	F+			
	aHR	**95% CI**		**p-value**
Date of enrollment				
2002-2004	ref			
2004-2006	0.63	0.42	0.94	0.023
2006-2008	1.17	0.76	1.83	0.476
2008-2011	1.60	0.92	2.80	0.100
Age (per year increase)	1.02	1.00	1.04	0.020
HIV stage*				
Stage I	ref			
Stage II	1.65	1.26	2.18	0.000
Stage III	2.40	1.77	3.26	<.0001
Pregnancy status				
Pregnant	3.12	2.33	4.17	<.0001
Not pregnant	ref			
Method of contraception				
Non-hormonal**	ref			
Implant	0.78	0.42	1.45	0.433
Injectables	0.72	0.46	1.12	0.145
OCPs	0.51	0.16	1.60	0.245
Genital Inflammation				
Yes (STI) 2	2.22	1.30	3.79	0.004
Yes (non-STI) 1	1.29	0.82	2.05	0.273
No	ref			
Genital ulceration				
Yes	1.41	0.96	2.08	0.085
No	ref			

aHR: hazard ratios from univariate Cox models
CI: confidence interval
p-values are 2-tailed from univariate Cox models
*No members had Stage IV HIV
330 outcomes modeled

Table 4a. Multivariate associations between covariates and disease progression for men including missingness variables

	M+			
	aHR	**95% CI**		**p-value**
Extrapulmonary TB				
Yes	0.08	0.01	0.653	0.020
No	ref			
ESR (per unit increase)^	1.03	1.02	1.04	<.0001

aHR: hazard ratios from univariate Cox models
CI: confidence interval
p-values are 2-tailed from univariate Cox models
*No members had Stage IV HIV
47 outcomes modeled
Adjusted for age, HIV stage, and genital inflammation

Table 4b. Multivariate associations between covariates and disease progression for women including missingness variables

	F+			
	aHR	**95% CI**		**p-value**
Log viral load (per log10 copies/ml increase)	1.67	1.25	2.24	0.001
ESR (per unit increase)^	1.00	0.99	1.01	0.797
TB				
Yes	24.31	2.35	252.03	0.008
No	ref			
Breastfeeding				
Yes	0.27	0.04	1.96	0.193
No	ref			

aHR: hazard ratios from univariate Cox models
CI: confidence interval
p-values are 2-tailed from univariate Cox models
Adjusted for date of enrollment, age, HIV stage, pregnancy status, method of contraception, genital inflammation, and genital ulceration
330 outcomes modeled

Discussion

In this study of Rwandan HIV discordant couples, we focused on biological and societal factors for why some individuals progress faster than others. We found HIV+ females to be more likely than HIV+ males to initiate ART therapy. One reason could be if females were more likely to seek treatment than men are more likely to be late presenters (Ndawinz et al., 2013). Additionally, women interact with the health care system more during pregnancy and may have been tested and initiated on ART via antenatal care (Larsen et al., 2019). The Larsen 2019 study looked at ART initiation in men and women within South Africa between 2014 and 2015. They found that less than 50% of men and non-pregnant women started ART in 14 days, while around 88% of pregnant woman initiated within 14 days (Larsen et al., 2019). We also found that HIV+ females were more likely to progress if they were pregnant. Females may initiate ART because they did not want to risk their child to be born with HIV or were recommended HIV treatment by physicians (WHO, 2020). It is not likely that women are more likely to die from HIV than men since both had similar death rates. This tells us there may be a behavioral or societal reason why females are more likely to seek treatment than men. We may need to have better outreach strategies to HIV+ men in Rwanda to allow more to access ART therapy. More studies will need to be done to understand why HIV+ males are not as likely to initiate ART therapy and if some social stigma exists among men to prevent them to seek treatment.

We found HIV+ men and women to have many exposures associated with disease progression. Older age was found to be associated with disease progression in women, but not men. A non-statistically significant association was found between men's age and disease progression. Age is likely associated with disease progression as HIV has a long incubation and infectious period (Luo et al., 2019). STI-related genital inflammation was statistically associated with HIV disease progression in women and non-statistically associated with men. There is a lack of evidence that supports HIV disease progression with our definition of STI-related genital inflammation (gonorrhea, chlamydia or trichomonas) because these infections are treatable, although there is evidence that shows these STIs to be associated with increased HIV viral shedding (Chun, Carpenter, Macalino, & Crum-Cianflone, 2013; Khaw, Richardson, Matthews, & Read, 2018). HIV stage is associated with disease progression for women, but not men, but as mentioned earlier, women were more likely to seek ART than men, and more studies on the treatment-seeking behaviors of men and women will need to be done to fully understand this.

Of these exposures of HIV+ women that were associated with disease progression, stage 3 HIV and pregnancy may influence a female's decision to start ART. Since stage 3 HIV is clinically AIDS, a woman may feel she needs to seek ART treatment (Prevention, 2019). Pregnancy was found to be associated with disease progression in our study, but this has not been replicated (Wall et al., 2016; Wall, Rida, et al., 2017). In the Wall 2016 study, which looked at the association of pregnancy, breastfeeding, and hormonal contraception with HIV disease progression in Zambia from 1994 to 2012, ART initiation was not included as an outcome, so it is possible that pregnancy is more associated with ART initiation than death for our disease progression definition. Pregnancy has been found to be a factor of negative outcomes in other diseases, such as HSV, rubella, and varicella, but there is a lack of evidence of pregnancy leading

to further HIV disease course, which further shows that pregnancy may be more related to ART initiation rather than death (Silasi et al., 2015). According the WHO, 82% of pregnant and breastfeeding HIV+ women are also receiving ART (WHO, 2019). Pregnancy may be more associated with ART initiation as women may not want to risk their newborn to HIV. One 2017 study that looked at pregnancy and HIV disease progression within Kenya, Rwanda, South Africa, Uganda, and Zambia from 2006 to 2011 found that CD4+ counts did not change during a woman's pregnancy (Wall, Rida, et al., 2017). This further shows that pregnancy may be associated with ART initiation but not death. One systematic review also did not find an association between pregnancy and disease progression after looking at different studies (Calvert & Ronsmans, 2015).

In our analysis, contraception use among women was not associated with disease progression, which was not found in a previous study that showed hormonal implants to be associated with disease progression in Zambian women (Wall et al., 2016). One randomized trial found that one hormonal contraception, intrauterine contraceptive device (IUD) was associated with disease progression (Stringer et al., 2009). The underlying exposure, progesterone, was thought to be associated with HIV acquisition and disease progression (Stringer et al., 2009). We did find that implants, injectables, and OCPs had non-statistically significant protective effects against disease progression relative to no method use. A systematic review agrees with the Wall 2016 study, mentioned previously, that injectables were associated with the protection of disease progression (Phillips et al., 2016). Both also found no association with oral contraceptives and disease progression, which we found as well (Phillips et al., 2016; Wall et al., 2016). In another study however, they did not find an association between hormonal contraception and disease progression among women who were currently not on ART (Whiteman et al., 2016).

One limitation of our study was our sample sizes for progression in HIV+ men, and estimates had wide confidence intervals. Another limitation is that we did not collect data on other potentially important factors such as drug addiction, nutrition, stress, and genetics which may also play a role in disease progression that we were unable to measure (Al-Jabri, 2007). Information bias for self-reported measures, for example alcohol intake, may be another limitation of this study, as participants may report a lower alcohol intake than stated.

Conclusions

Females are more likely than males to initiate ART, but there are no differences between the outcome of death between males and females. We recommend outreach to males for ART initiation since this group. We also need to further understand why males are less likely to start ART.

Age was an association found for both men and women with HIV progression. For females there were additional association between date of enrollment, HIV stage, pregnancy status, and genital inflammation. There was no association between contraception methods and disease progression, so it should be safe for HIV-infected females to use implant, injectables, and OCPs to prevent pregnancy. Since we found HIV progression (more likely ART initiation) to be associated with pregnancy, we would expect a decrease in mother to child HIV transmission.

Chapter 3

Public Health Recommendations

We found that women have higher rates of ART initiation than men, which shows we need to have better outreach strategies to HIV+ men in Rwanda to allow more to access ART therapy as well as better understand why men are less likely to initiate ART. Since age was associated with disease progression in both men and women, older individuals should be a population for outreach prioritized for ART as well. We also found that it is safe for HIV-infected women to use hormonal contraception, such as implants, injectables, and OCPS, to prevent pregnancy.

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